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EXAMINER	
BRISTOL, LYNN ANNE	

ART UNIT	PAPER NUMBER
1643	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/533,503	BADACHE ET AL.	
	Examiner	Art Unit	
	LYNN BRISTOL	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 December 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-6,8,10-26 and 31-36* is/are pending in the application.

4a) Of the above claim(s) *17-26 and 31-36* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6,8 and 10-16* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1-6, 8, 10-26 and 31-36 are all the pending claims for this application.

2. Claims 17-26 and 31-34 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 5/12/08.

3. Claims 7 and 9 were cancelled, Claims 2, 6, 10, 13, 15, and 16 were amended and new Claims 35 and 36 were added in the Response of 12/3/08.

4. Newly submitted claims 35 and 36 directed to an invention that is independent or distinct from the invention originally claimed for the following reasons: The elected claims under examination are drawn to a method for identifying Stat3-dependent cell proliferation modulating agents using TEL/Etv6 as a target substrate while New Claims 35 and 36 are drawn to a method for identifying modulating agents for enhancing cytokine-induced inhibition of cell proliferation using TEL/Etv6 as a target substrate. Under MPEP MPEP § 806.05(j), the methods have a different intended population and thus a different effective outcome, therefore the inventions as claimed do not encompass overlapping subject matter and there is nothing of record to show them to be obvious variants.

Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claims 35 and 36 are withdrawn from

consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

5. Claims 1-6, 8 and 10-16 are all the pending claims under examination.

6. Applicants amendments to the claims have necessitated new grounds for objection and rejection. This action is FINAL.

Withdrawal of Objections

Claim Objections

7. The objection to Claim 10 for reciting “the test compound” is withdrawn in view of the amendment in the Response of 12/3/08 to more consistently recite “the compound.”

8. The objection to Claim 16 for reciting "can be observed as a reduction of reporter gene expression" is withdrawn in view of the amendment in the Response of 12/3/08 to recite the reporter gene expression being from the reporter gene construct.

Withdrawal of Rejections

Claim Rejections - 35 USC § 112, second paragraph

9. The rejection of Claims 1-5 as being incomplete for omitting essential steps, i.e., the step of identifying the modulating effect of the test compound selected in step iii) of Claim 1 on Stat3-dependent cell proliferation, is withdrawn.

Applicants allege on p. 9 of the Response of 12/3/08 "The step iii) of claim 1 requires determining a compound-induced modulation in the TELfl/tv6 activity relative to when said compound is absent".

10. The rejection of Claims 6-9, 11-13, 15 and 16 as being incomplete for omitting essential steps, i.e., a) the nexus between the binding agent, TEL/Etv6 and Stat3 in Claim 6, b) the step of identifying the modulating effect of the test compound selected in step ii) of Claim 6 on Stat3-dependent cell proliferation and c) the nexus for reporter gene expression upon contact between TEL/Etv6 and the binding partner to Stat3-dependent cell proliferation in Claim 16, is withdrawn.

Applicants allege on p. 9 of the Response of 12/3/08 "step (ii) of claim 6 requires determining whether the presence of a test compound modulates the interaction between said TEL/Etv6 polypeptide and the binding partner relative to when the test compound is absent".

11. The rejection of Claim 2 for the recitation "said agent is effective in enhancing cytokine-induced inhibition of cell proliferation" is moot in view of the amendment in the Response of 12/3/08 to delete the phrase.

12. The rejection of Claim 7 for the recitation "wherein the variant or fragment of TEL/Etv6 has the ability to bind Stat3" is moot for the cancelled claim.

13. The rejection of Claim 13 in lacking antecedent basis for the limitation "the substance" is withdrawn in view of the amendment in the Response of 12/3/08 to recite "test compound."

14. The rejection of Claim 15 [originally Claim 16 in error] for the recitation in element (ii) "identifying substances which inhibit said interaction in said cell" is withdrawn in view of the amendment in the Response of 12/3/08 to recite "the compounds."

Objections Maintained

Specification

15. The objection to the disclosure for failing to include the relationship to PCT/EP03/12295 (11/4/03) and its priority claim to GB 0225799.6 (8/14/02) is maintained. Applicants have enclosed a request to amend the cross-reference section of the specification in the Response of 12/3/08 but the amendment is non-compliant under 37 CFR § 1.121, as amended on June 30, 2003 (see *68 Fed. Reg. 38611*, Jun. 30, 2003) See 37 CFR 1.121 section (b) (1) (ii) "The full text of any replacement paragraph with markings to show all the changes relative to the previous version of the paragraph. The text of any added subject matter must be shown by underlining the added text. The text of any deleted matter must be shown by strike-through except that double brackets placed before and after the deleted characters may be used to show deletion of five or fewer consecutive characters. The text of any deleted subject matter must be shown by being placed within double

brackets if strikethrough cannot be easily perceived;...".

16. The objection to the use of trademarks, e.g., GeneChips™ noted in this application is maintained.

Applicants have stated on p. 9 of the Response of 12/3/08 that "they will amend the specification, prior to issuance, to properly identify the trademarks."

Rejections Maintained

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

17. The rejection of Claim13 for the recitation "confirming the substance inhibits cell proliferation of a cytokine-sensitive cancer" because the recitation is broader than the generic method of Claim 6 for determining that the test compound is an agent effective in modulating Stat3-dependent cell proliferation. Alternatively, what is the correlation between Stat3-dependent cell proliferation and cytokine-dependent cell proliferation?"

Applicants allegations on p. 10 of the Response have been considered and are not found persuasive. Applicants allege "Claim 6 provides for a method of identifying an agent effective in modulating s ta.t3-dependent cell proliferation. It, therefore, provides a starting point for narrowing down an unlimited number of possible agents to a finite number of possible agents effective for modulating stat3-dependent cell proliferation.

Claim 13 further limits claim 6 by requiring the step of confirming that the substance in fact inhibits cell proliferation of a cytokine-sensitive cancer."

Response to Arguments

Generic Claim 6 does not require that the assay be performed in a cell, only, that the ordinary artisan would measure the interaction between TEL and Stat3 in the presence of a test compound. Claim 13 requires that any test compound found to inhibit an interaction between TEL and Stat3 is further tested in any cytokine-sensitive cancer, irrespective of whether that cytokine-sensitive cancer expresses both Stat3 and TEL. Claim 13 encompasses any cytokine-responsive cancer and provides no correlation between the preceding method steps requiring an interaction between TEL/Stat3 and the step of further measuring the compound in a proliferation assay.

Claim Rejections - 35 USC § 112, first paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Biological Deposit

18. The rejection of Claims 15 and 16 under 35 U.S.C. § 112, first paragraph, because the specification does not enable a cell or cell line expressing a TEL/Etv6 variant or a fragment thereof which has the ability to interact with a Stat3 variant or fragment thereof is known and publicly available, or can be reproducibly isolated without undue experimentation is maintained.

Applicants' allegations on pp. pp. 11-13 of the Response of 12/3/08 have been considered and are not found persuasive. Applicants allegations address the original rejection for a cell line expressing only a TEL/Etv6 variant or fragment, which as conceded to by the examiner, the specification teaches constructs for TEL mutants: TELΔ41-127 (i.e. AP), TELΔ122-176, TELΔ122-217, TELΔ268-333, TELΔ303-333, TELΔ333-352, TELΔ442-452, TELDBDM (R396K; R399K) that are transfected into "Stat3-ER-A375 cells and HEK 293 cells" (p. 36, ¶3-4).

The claims have been amended in the Response of 12/3/08 to recite that the cell should express any TEL/Etv6 variant or fragment thereof in addition to any Stat3 variant or fragment thereof, where there is no example of any such cell defined in the specification or art having both a functional TEL variant or fragment and a functional Stat3 variant or fragment. Applicants' specification does not define an example of a Stat3 variant or fragment thereof that can be cloned into an expression vector and co-expressed in a cell comprising a TEL/Etv6 variant or fragment and that could be used in the instant claimed method. The specification teaches Stat 3 variants at:

p. 5, ¶3, " As those skilled in the art will appreciate, unless context demands otherwise, where polypeptides or nucleic acids are referred to in aspects and embodiments of the invention disclosed herein (e.g. TEL, Stat3) variants (e.g. derivatives or homologues) of the polypeptides or nucleic acids may also be used in the present invention, provided that they still encode the requisite activity. Generally speaking such variants will be substantially homologous to the ~vild type' or other sequence specified herein i.e. will share sequence similarity or identity therewith. Similarity or identity may be at the nucleotide sequence and/or encoded amino acid sequence level, and will preferably, be at least about 50%, 60%, or 70%, or 80%, most preferably at least about 90%, 95%, 96%, 97%, 98% or 99%. Sequence comparisons may be made using FASTA and FASTP (see Pearson & Upman, 1988. Methods in Enzymology 183: 63-98). Parameters are preferably set, using the default matrix, as follows: Gapopen (penalty for the first residue in a gap): -12 for proteins/-16 for DNA; Gapext (penalty for additional residues in a gap): -2 for proteins 1-4 for DNA; KTUP word length: 2 for proteins / 6 for DNA.

Analysis for similarity can also be carded out using hybridisation. One common formula for calculating the stringency conditions required to achieve hybridization between nucleic acid molecules of a specified sequence homology is: Tm = 81.5 C + 16.6Log [Na+] + 0.41 (% G+C) - 0.63 (% formamide) - 600/#bp in duplex Molecular Cloning: a Laboratory Manual: 2nd edition, Sambrook et al., 1989, Cold Spring Harbor Laboratory Press)",

and

p. 7, ¶4 "As exemplified below in Example 9, the binding partner may be Stat3, a variant or fragment thereof."

Notably, Example 9 does not define an example of a Stat3 variant or fragment thereof that possesses a requisite functional activity because Applicants have not shown which domain in the full length Stat3 gene promoter much less the actual full length Stat3 protein is required for binding or interaction with TEL/Etv6.

Enablement

19. The rejection of Claims 1-6, 8, and 10-16 under 35 U.S.C. 112, first paragraph, is maintained because the specification does not reasonably provide enablement for: correlating the modulation of any TEL activity in the presence of any test agent to Stat3-dependent cell proliferation, or the binding of TEL protein to Stat3 protein much less to any Stat3 variant or fragment thereof irrespective of whether the test agent is present.

For review, the rejection was set forth in the Office Action of 9/3/08 as follows:

"Nature of the Invention/ Skill in the Art

Claims 1-5 and 10 are *interpreted* as being drawn to a method for identifying modulating agents for Stat3-dependent proliferation and where the agent is selected on the basis of the steps comprising incubating TEL/Etv6 and a compound, detecting TEL/Etv6 modulation in the presence and the absence of the compound in order to compare whether there is an alteration in the TEL/Etv6 activity, where the alteration in activity by the compound indicates that it would be an effective modulator of Stat3-dependent cell proliferation (Claim 1), where modulation of TEL is measured as inhibition of its activity and the agent enhances cytokine-induced inhibition of cell proliferation (Claim 2), where modulation of TEL is measured as activation of its activity and the agent inhibits Stat3-expressing

cell proliferation and Stat3 is phosphorylated (Claim 3), where cell proliferation in Claim 3 is ras-independent (Claim 4), where cell proliferation is for a melanoma or carcinoma (Claim 5), and the method further comprises determining whether the compound modulates Stat3-dependent cell proliferation (Claim 10).

Claims 6-9 and 11-16 are *interpreted* as being drawn to a method for identifying modulating agents for Stat3-dependent proliferation and where the agent is selected on the basis of the steps comprising incubating TEL/Etv6 or a variant or fragment thereof, a binding partner and a test compound and determining whether in the presence or absence of the test compound a change or modulation for the interaction between the TEL/Etv6 protein and the binding partner occurs (Claim 6), where the variant or fragment of TEL/Etv6 binds Stat3 (Claim 7), where the fragment of Claim 7 is between 50 and 350 amino acids in length (Claim 8), where the binding partner of Claim 6 is Stat3, a variant or fragment thereof (Claim 9), the TEL/Evt6 polypeptide or binding partner of Claim 6 is labeled with a detectable label and the other is immobilized on a solid support (Claim 11), where the modulation in Claim 6 involves inhibiting the interaction (Claim 12), where the method of claim 12 confirms that the test compound inhibits proliferation of a cytokine-sensitive cancer (Claim 13), where the test compound of Claim 12 is examined for whether it inhibits the physical association between TEL/Etv6 and Stat3 (Claim 14), where the method of Claim 6 further comprises contacting a test compound with a cell expressing the TEL/Etv6 polypeptides which can interact with the binding partner and identifying compounds that inhibit the interaction between the TEL/Etv6 polypeptide and the binding partner in the cell (Claim 15), and where the method of Claim 15 comprises a cell expressing the TEL/Etv6 polypeptide, the binding partner and a reporter gene construct and contacting the cell with a test compound in order to inhibit binding between TEL/Etv6 polypeptide and the binding partner and where the inhibition is observed by a reduction in reporter gene expression (Claim 16).

The relative skill in the art for practicing the method is a skilled technician in a high throughput drug screening lab with a background in second messenger signaling mechanisms relating to gene transcription in cell proliferation.

Disclosure in the Specification/ Undue Experimentation

The following working embodiments are disclosed and accordingly are enabling for the scope of a method drawn to the steps described in each of the examples:

Example 6: The specification describes an experiment were performed to investigate the function of TEL in Stat3-mediated inhibition of cell proliferation essentially as described in Example 4 but using TEL siRNA nt 540-560, 5'-CCCUCCCACCAUUGAACUGdTdT-3' (SEQ ID NO:4) and 5'-CAGUUCA AUGGUGGGAGGGdTdT-3' (SEQ ID NO:5). This Example follows cell proliferation of Stat3-ER-expressing A375 cells treated with 4HT or a combination of 4HT and OSM, and in the absence or in the presence of siRNA to TEL. The specification states "TEL was strongly increased upon 4HT or 4HT/OSM treatment. This increase was largely prevented in the presence of TEL siRNA. Surprisingly, in the presence of TEL siRNA, Stat3-mediated inhibition of A375 cell proliferation was significantly increased (from about 28% to about 40%). Stat3-dependent transcription of luciferase, induced by 4HT or OSM, was significantly increased (from about 6 to 16 fold increase over control, and from about 9 fold to 18 fold increase over control respectively) when TEL expression was reduced by siRNA." The specification states "the inhibition of breast carcinoma and melanoma cell proliferation by IL-6-type cytokines, as exemplified here with A375 cells, is dependent on Stat3 activity, which can be induced by reducing TEL activity." **No data from this experiment are shown in the application as filed.**

Example 7: The specification describes an experiment in which TEL- or control, pcDNA3.1-transfected Stat3ERA375 cells, treated with 4HT were cultured in the presence or absence of Trichostatin A (TSA; 250 nM), a general HDAC inhibitor. Addition of TSA to 4HT-stimulated cells prevented the repression of Stat3 activity by TEL, but had no effects on Stat3 mediated transcriptional activity in pcDNA3.1-transfected cells. **No data from this experiment are shown in the application as filed.**

Example 8: The specification describes an experiment in which Stat3-ER-A375 cells and HEK 293 cells were transfected with the different TEL mutants, a Stat3 reporter plasmid and a Renilla plasmid. Cells were treated with 4HT or OSM for 24 h and luciferase activity was measured using the luciferase assay described in Example 1. Only TEL .DELTA.P, missing the pointed domain, failed to repress Stat3 activity. TEL delta 333-452 represses Stat3 activity, whereas TEL delta 442-452 is not able to repress Stat3 activity. TEL, TEL delta P, TEL delta 333-452 and to a less extent TEL delta 442-452 still interact with Stat3. **No data from this experiment are shown in the application as filed.**

Example 9: The specification describes an experiment in which extracts from nuclear-enriched fractions were prepared from control or OSM-stimulated A375 cells. Antibody probing nuclear lysates reveals the expected increase in Stat3 levels following OSM treatment, while the nuclear content of TEL is not affected by OSM. Endogenous TEL was present in Stat3 immunoprecipitates and the levels of TEL associating with Stat3 increased in OSM-treated compared to control-treated nuclear extracts. Conversely, Stat3 is present in a TEL-containing complex, pulled down through an immobilized GGM-containing oligonucleotide, which is a binding site for TEL. **No data from this experiment are shown.**

The conclusions that Applicants draw from these studies are that TEL is a transcriptional repressor of Stat3 transcriptional activity by interacting with Stat3 directly and recruiting HDACs to the Stat3 transcriptional complex.

Notably, in order to have fully evaluated the disclosure, the examiner was required to resort to the post-filing date publication by the inventors (Schick et al. (J. Biol. Chem. 279(37):38787-38796 (2004); cited in the IDS of 4/17/07) showing these same data in table and figure format.

The examiner's position is that the specification demonstrates TEL acts as a repressor or negative regulator of Stat3 transcriptional activity and whose repressor activity is further dependent on recruitment of a co-repressor complex, comprising mSin3A, NcoR and SMRT, which are known to interact with histone deacetylases (HDACs) [0127]. Thus it is not predictable that the binding of TEL alone to Stat3 would inhibit Stat3 transcriptional activity, or that any test compound could inhibit this interaction to modulate Stat3 transcriptional activity measured by cell proliferation.

Applicants have demonstrated with a single compound, Trichostatin A, that TEL repressor activity for Stat3-mediated transcriptional activity could be blocked in the A375 cell line. Applicants have demonstrated TEL repressor activity for Stat3 transcriptional activity in a transfected cell line A375 carrying a Stat3_ER reporter construct and in the HEK 293 cell line.

Applicants have not demonstrated the universality of Stat3 regulation of cell proliferation in any cell much less any cancer cell. Applicants have not demonstrated the universality for the repressor activity of TEL for Stat3 transcriptional activity in any cell line much less any cancer cell line. Applicants have not demonstrated that TEL/ETv6 has the universe of binding partner(s) encompassed by the claims. Thus the specification is not enabling for screening drugs where modulation or alteration of any TEL activity is correlative with modulating Stat3-dependent cell proliferation in any cell much less any cancer cell.

The ordinary artisan would be required to perform undue experimentation in order to identify the universe of TEL/Etv6 activities and the universe of TEL/Etv6 binding partners encompassed by the claims to practice the method scope in assessing whether the universe of test agents/test compounds would positively or negatively affect any TEL/ETv6 activity or binding property to then correlate this change with Stat3-dependent cell proliferation.

Applicants' allegations on pp. 13-15 of the Response of 12/3/08 have been considered and are not found persuasive.

A) Applicants allege the specification provides a series of examples demonstrating a nexus between inhibiting TEL expression and Stat3 activity." For instance, Example 6 shows TEL is a Stat3-induced negative regulator of Stat3 activity, Example 7 shows trichostatin A inhibits repression of Stat3 activity by TEL, and Example 9 shows that Stat3 is present in a TEL-containing complex pulled down through an immobilized GGAA-containing oligonucleotide that binds TEL, suggesting that TEL interacts directly with Stat3 and recruits HDAC to the Stat3 transcriptional complex when repressing Stat3 transcriptional activity.

Response to Arguments

i) Claims 1-5 are not limited to assaying the test compound for having a direct effect on TEL/Etv6 and Stat3 interaction or Stat3 activity. The only requirement is to measure *any* TEL/Etv6 activity without specifying what that activity is. For example, in the Schick reference cited in the previous Office Action (and authored by the instant inventors), it teaches that "TEL-44 inhibits transformation of NIH-3T3 fibroblasts by Src" (p. 38795, Col. 1 to Col.2).

Thus, it is not even clear that TEL/Etv6 regulates only Stat3. The instant inventors already acknowledge that the art recognizes TEL/Etv6 as having pleiotropic activity, e.g., regulating other gene(s) or activities of the expressed gene, thus the instant claimed method is not enabled in its specificity or exclusivity for identifying a compound that necessarily would also modulate Stat3-dependent cell proliferation. The only requirement of Claims 1-5 is that any change in TEL/Etv6 activity in the presence of the compound is "*indicative* of an agent effective in modulating Stat3-dependent cell proliferation".

ii) Further and as previously stated in the Office Action, Schick teaches: "The repressive activity of TEL has previously been shown to depend on recruitment of a co-represser complex comprising mSin3A, NcoR, and HDACs to distinct TEL domains (27, 38, 44, 45). These include the C-terminal pointed domain, which is necessary for TEL oligomerization and association with other proteins (36, 45, 46); the N-terminal ETS domain, which inter\- acts with specific DNA elements but also mediates protein~ protein interactions (27, 46, 47); and the central TEL region, spanning amino acid residues 268-333, that associates with HDAC3 (27). We show here that TEL-mediated

repression of Star3 is dependent on HDAC activity and that the TEL pointed domain, but not the central region, is required for this repression."

Claims 6, 8 and 10-16 require incubating at least one polypeptide of TEL/Etv6 or a variant or fragment thereof with Stat3, a variant of fragment thereof in the presence of a test compound, where the other elements taught and appreciated by Applicants are excluded from the method assay. Applicants have not shown that TEL/Etv6 much less a variant or fragment thereof and Stat3 much less a variant or fragment thereof can directly bind to each other in order to practice the method invention. Applicants have not shown and Schick et al. do not even suggest that there is one-to-one protein interaction or direct physical association between TEL/Etv6 and Stat3. In the absence of the other elements of the co-repressor complex, it is not predictable that the method could be practiced in the manner reasonably correlated with the instant method claim scope.

B) Applicants allege "With respect to the Examiner's argument relating to the universe of binding partner(s) encompassed by the claim, Applicants have amended claim 6 to change from "a binding partner" to "Star3, a variant or fragment thereof"."

Response to Arguments

Claims 6, 8 and 10-16 have been amended in the Response of 12/3/08 to recite that the cell should express any TEL/Etv6 variant or fragment thereof in addition to Stat3 or any Stat3 variant or fragment thereof, where there is no example of any such cell defined in the specification or art having both a functional TEL variant or fragment and a functional Stat3 variant or fragment.

Applicants' specification does not define an example of a Stat3 variant or

fragment thereof that can be cloned into an expression vector and co-expressed in a cell comprising a TEL/Etv6 variant or fragment and that could be used in the instant claimed method.

Applicants do not define an existing example of a Stat3 variant or fragment thereof with known interacting properties for TEL/Etv6. The specification teaches Stat 3 variants at:

p. 5, ¶3, " As those skilled in the art will appreciate, unless context demands otherwise, where polypeptides or nucleic acids are referred to in aspects and embodiments of the invention disclosed herein (e.g. TEL, Stat3) variants (e.g. derivatives or homologues) of the polypeptides or nucleic acids may also be used in the present invention, provided that they still encode the requisite activity. Generally speaking such variants will be substantially homologous to the ~vild type' or other sequence specified herein i.e. will share sequence similarity or identity therewith. Similarity or identity may be at the nucleotide sequence and/or encoded amino acid sequence level, and will preferably, be at least about 50%, 60%, or 70%, or 80%, most preferably at least about 90%, 95%, 96%, 97%, 98% or 99%. Sequence comparisons may be made using FASTA and FASTP (see Pearson & Upman, 1988. Methods in Enzymology 183: 63-98). Parameters are preferably set, using the default matrix, as follows: Gapopen (penalty for the first residue in a gap): -12 for proteins/-16 for DNA; Gapext (penalty for additional residues in a gap): -2 for proteins 1-4 for DNA; KTUP word length: 2 for proteins / 6 for DNA. Analysis for similarity can also be carded out using hybridisation. One common formula for calculating the stringency conditions required to achieve hybridization between nucleic acid molecules of a specified sequence homology is: Tm = 81.5 C + 16.6Log [Na+] + 0.41 (% G+C) - 0.63 (% formamide) - 600/#bp in duplex Molecular Cloning: a Laboratory Manual: 2nd edition, Sambrook et al., 1989, Cold Spring Harbor Laboratory Press)",

and

p. 7, ¶4 “As exemplified below in Example 9, the binding partner may be Stat3, a variant or fragment thereof.”

Notably, Example 9 does not define an example of a Stat3 variant or fragment thereof that possesses a requisite functional activity because Applicants have not shown which

domain in the full length Stat3 gene promoter much less the actual full length Stat3 protein is required for binding or interaction with TEL/Etv6. Further and as discussed above, Applicants specification has not shown and Schick et al. do not even suggest that there is direct one-to-one protein interaction or direct physical association between TEL/Etv6 and Stat3.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

20. The rejection of Claims 1, 2, and 5 under 35 U.S.C. 103(a) as being unpatentable over Chakrabarti et al., (Biochem. Biophys. Res. Comm., (1999) 264:871-877; cited in the IDS of 4/17/07) in view of Dong et al., Blood (2002) 99(8):2637-2646; cited in the PTO 892 form of 4/10/08) and further in view of Kortylewski et al. (Oncogene 18:3742-3753 (1999); cited in the IDS of 4/17/07) is maintained.

For purposes of review, the rejection was set forth in the Office Action of 9/3/08 as follows:

"The claimed method inventions were prima facie obvious at the time of the invention over Chakrabarti, Dong and Kortylewski.

Chakrabarti discloses TEL is a DNA-binding, transcriptional repressor which involves the recruitment of a repressor complex including SMART, SIN3A, N-CoR and which is further mediated through histone deacetylases. When the histone deacetylase inhibitor, TSA, is added to the mix in a reporter gene assay using yeast transcription activator Gal4 in NIH-3T3 or COS7 cells, repression by TEL and truncation variants thereof were inhibited by TSA. The results show TEL recruits components of a repressor complex at the promoter site and such complexes are postulated for other transcription factors which interact with co-repressors. Chakrabarti discloses that the activity described for TEL could be a common mechanism of alteration of gene transcription leading to neoplastic transformation and cancer.

Dong examined the transcriptional activity for Stat3 using Stat3 reporter gene constructs and found that SMRT and CoR are recruited with Stat5 for regulating Stat3 activity.

Kortylewski teaches that members of the IL-6 family of cytokines including IL-6, OSM, LIF and CNF have been shown to inhibit proliferation of some leukemia, melanoma, prostate and breast cancer cells and this inhibition is mediated by Stat3, and that in some cellular contexts, Stat3 has anti-proliferative and anti-oncogenic effects. Kortylewski teaches with receptor chimeras and dominant negative forms of Stats that growth-arrest of human A374 melanoma cells depends on Stat3.

One skilled in the art would have been motivated and been reasonably assured of success in having produced a method for screening drugs that modulate Stat3 dependent growth by measuring the drug effect on TEL/Etv6 activity at the time of the invention over Chakrabarti, Dong and Kortylewski. Chakrabarti and Dong establish the nexus between Stat3 and TEL as comprising or sharing SMRT and Co-R, where TEL in combination with these co-factors had been recognized as having repressor function in transcription activity for many different genes and the potential role in regulating cell proliferation, and Dong shows that Stat3 transcriptional activity is affected by SMRT and Co-R in reporter gene assays with Stat5. Dong appreciates that Stat3 has been shown in some signaling pathways as being an oncogene whereas under other conditions is anti-oncogenic, and Kortylewski teaches and appreciates the anti-oncogenic effect of the IL-6 family of cytokines mediating the down-regulation of cell proliferation thru Stat3. Because it was known that TEL was a repressor of transcriptional activity for many genes and regulation of Stat3 activity was possible because of the shared co-factors between TEL and Stat5, one skilled in the art would have been motivated to have formulated a method assay for screening drugs that modulated the activity of TEL (or its binding with SMRT or Co-R) in order to modulate the activity of Stat3 because of the motivation provided in the references to identify mechanisms for regulating cytokine-mediated cell proliferation which affect Stat3. One skilled in the art would have been reasonably assured of success in practicing the method assay because of the availability of the reagents, reporter gene constructs, variants for TEL, variants for Stat3 and the nexus between the cytokine-mediated downregulation of cell prolfiferation occurred thru Stat3 and TEL being a negative repressor for transcpriotnal activity for many genes involved in transformation and oncogenesis. The method inventions were prima facie obvious over Chakrabarti, Dong and Kortylewski."

Applicants' allegations on pp. 15-17 of the Response of 12/3/08 have been considered and are not found persuasive. Applicants allege "The fact that Charkrabarti and Dong et al. in combination teach that TEL/Etv6 and Stat3 share common co-repressors such as SMRT and COR does not by itself render obvious the relationship between TEL/Etv6 and Stat3. There are other factor(s) that are involved in Stat3-dependent cell proliferation, namely HDAC, which Dong et al. does not disclose. In

addition, the role of Stat3 in cell proliferation is unclear as the prior art has shown Stat3 to be an oncogene in some instances while also being a mediator of cytokine-induced inhibition of tumor cell proliferation in other instances. As such, one skilled in the art would not have formulated a screening method that modulates TEL/Evt6 activity or the interaction between TEL/Etv6 and Stat3 and have an expectation of success in Stat3-dependent cell proliferation."

Response to Arguments

Contrary to Applicants assertion, Dong defines "CoR" as comprising SMRT/NCoR, Sin3 and histone deactylase (HDAC) (p. 2638, Col. 1, ¶2), and therefore, the elements of Dong are similar to the elements of Charkrabarti.

Secondly, Applicants' assertion regarding the different "art recognized" biological properties of Stat3 on cell proliferation, are not supported by citation to any reference authority and is proffered as common knowledge. Pursuant to MPEP 2144.03, "ordinarily there must be some form of evidence in the record to support an assertion of common knowledge."

Finally, Applicants recite a veritable list of "effects" (i)-(v) (bottom of p. 16 of the Response of 12/3/08) which they have observed "only through meticulous experimentations of the current inventors". It is noted that the features upon which applicant relies (i.e., elements (i)-(v)) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

New Grounds for Objection

Claim Objections

21. Claims 12 and 14 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claim 12 is drawn to the method of Claim 6 where the modulation by the test compound is inhibition of the interaction between TEL/Etv6 and Stat3 or the corresponding variant or fragment thereof. Claim 14 is drawn to the method of Claim 12 where the test compound is measured for inhibiting the physical association between TEL/Etv6 and Stat3. The claimed subject matter is not considered to be further limiting and the specification does not define a qualitative and/or quantitative difference between the terms "interaction" and "physical association".

New Grounds for Rejection

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

22. Claim 11 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 11 recites the limitation "the binding partner". There is insufficient antecedent basis for this limitation in the claim and in Claim 6 from which the claim depends.

Conclusion

23. No claims are allowed.

24. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

25. Any inquiry concerning this communication or earlier communications from the examiner should be directed to LYNN BRISTOL whose telephone number is (571)272-6883. The examiner can normally be reached on 8:00-4:30, Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on 571-272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

LAB

/David J Blanchard/
Primary Examiner, Art Unit 1643